

Lower cardiorespiratory fitness contributes to increased insulin resistance and fasting glycaemia in middle-aged South Asian compared with European men living in the UK

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Abstract

Aims/hypothesis This study aimed to determine the extent to which increased insulin resistance and fasting glycaemia in South Asian men, compared with white European men, living in the UK, was due to lower cardiorespiratory fitness (maximal oxygen uptake [$\dot{V}O_{2max}$]) and physical activity. **Methods** One hundred South Asian and 100 age- and BMI-matched European men without diagnosed diabetes, aged 40–70 years, had fasted blood taken for measurement of glucose concentration, HOMA-estimated insulin resistance ($HOMA_{IR}$), plus other risk factors, and underwent assessment of physical activity (using accelerometry), $\dot{V}O_{2max}$, body size and composition, and demographic and other lifestyle factors. For 13 South Asian and one European man, HbA_{1c} levels were $>6.5\%$ (>48 mmol/mol), indicating potential undiagnosed diabetes; these men were excluded from the analyses. Linear regression models were used to determine the extent to which body size and composition, fitness and physical activity variables explained differences

in $HOMA_{IR}$ and fasting glucose between South Asian and European men.

Results $HOMA_{IR}$ and fasting glucose were 67% ($p<0.001$) and 3% ($p<0.018$) higher, respectively, in South Asians than Europeans. Lower $\dot{V}O_{2max}$, lower physical activity and greater total adiposity in South Asians individually explained 68% (95% CI 45%, 91%), 29% (11%, 46%) and 52% (30%, 80%), respectively, and together explained 83% (50%, 119%) (all $p<0.001$) of the ethnic difference in $HOMA_{IR}$. Lower $\dot{V}O_{2max}$ and greater total adiposity, respectively, explained 61% (9%, 111%) and 39% (9%, 76%) (combined effect 63% [8%, 115%]; all $p<0.05$) of the ethnic difference in fasting glucose. **Conclusions/interpretation** Lower cardiorespiratory fitness is a key factor associated with the excess insulin resistance and fasting glycaemia in middle-aged South Asian, compared with European, men living in the UK.

Keywords Adiposity · Ethnicity · Fitness · Glycaemia · Insulin resistance · Maximal oxygen uptake · Obesity · Physical activity · Sedentary · South Asian

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Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CRP	C-reactive protein
CURVES	Carotid Ultrasound and Risk of Vascular disease in Europeans and South Asians study
GGT	γ -Glutamyltransferase
$HOMA_{IR}$	HOMA-estimated insulin resistance
MVPA	Moderate-to-vigorous physical activity
SES	Socioeconomic status
SIMD	Scottish Index of Multiple Deprivation
$\dot{V}O_{2max}$	Maximal oxygen uptake

Introduction

South Asians living in the UK have a three- to fivefold increased prevalence of type 2 diabetes and develop the disease around a decade earlier and at a lower BMI compared with white Europeans [1, 2]. In addition, non-diabetic South Asians exhibit higher glucose levels than Europeans [3, 4]. While the mechanisms for their higher risk are not fully understood, greater insulin resistance is a strong candidate [3, 5, 6].

Adiposity [7–9], cardiorespiratory fitness [8, 10] and physical activity [11, 12] are key factors influencing insulin resistance, glycaemia and diabetes risk. South Asians carry more body fat than Europeans and this may be distributed more centrally [5, 13, 14]. However, it appears that South Asians remain more insulin resistant than Europeans after matching or adjustment for a range of adiposity markers [6, 9]. Furthermore, limited data from small studies suggest that cardiorespiratory fitness, as assessed by maximal oxygen uptake ($\dot{V}O_{2\max}$), is 10–20% lower in South Asians than in matched Europeans [6, 15, 16], with our previous data [6] showing that adjustment for $\dot{V}O_{2\max}$ attenuated the difference in insulin sensitivity between young South Asian and European men. In addition, habitual levels of physical activity among South Asians living in the UK appear lower than in Europeans [17–20]. Low physical activity has been shown to explain part of the excess cardiovascular disease risk observed in South Asians [18], and could conceivably contribute to their increased diabetes risk. However, the data available on physical activity in South Asians have been obtained from self-reported questionnaires; these have limited validity compared with objective measures [21, 22], and this is potentially exacerbated in South Asians because of cultural interpretation of the terminology used in the questionnaires [17]. Misclassification arising from the use of questionnaires to assess physical activity can substantially underestimate the true relationship between activity and risk of vascular and metabolic disease [23, 24].

Thus, from the available data, the extent to which lower cardiorespiratory fitness and lower physical activity contributes to increased insulin resistance and glycaemia in South Asians is not established. We hypothesised that these factors would explain a substantial proportion of the increased insulin resistance and glycaemia observed in South Asian men living in the UK.

Methods

Participants and recruitment All participants (100 South Asians, 100 Europeans) were recruited to the Carotid Ultrasound and Risk of Vascular disease in Europeans and South Asians (CURVES) study, which had the primary aim of

comparing prevalence of, and risk factors for, carotid atherosclerotic plaques between middle-aged South Asian and European men. South Asians (defined as having both parents of Indian, Pakistani, Bangladeshi or Sri Lankan origin) and European (both parents of white European origin) men, aged 40–70 years, without coronary heart disease (symptoms of angina, previously labelled ischaemic heart disease, previous myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty), cerebrovascular disease, peripheral vascular disease or known diabetes were recruited to undertake a number of cardiometabolic investigations as described below. Individuals with musculoskeletal or other disorders (e.g. significant respiratory or circulatory disorder) that would prevent treadmill exercise testing were also excluded.

Volunteers were recruited via: (1) local advertising/word-of-mouth; and (2) by writing to potentially eligible participants identified from four local primary-care practice databases. The majority of participants (95 South Asians and 93 Europeans) were recruited by method (1). Using method (2), 470 potential volunteers (220 South Asians and 250 Europeans) meeting the study inclusion criteria were identified and sent letters inviting their participation. Fifteen individuals (seven South Asians, eight Europeans) replied positively. Three of these individuals did not respond to further attempts at contact: thus, 12 participants (five South Asians, seven Europeans) were recruited to the study by method (2). Participants were given feedback on their personal health data and received £20 to cover travel/transport costs, but no other participation incentive. All participants were resident and registered with a primary-care physician in Scotland. The study was approved by the West of Scotland Research Ethics Committee and conducted according to the principles expressed in the Declaration of Helsinki. All participants gave written informed consent.

Participants' health history, including smoking status and family health history, was determined by questionnaire. Years of education was determined by questionnaire. Socio-economic status (SES) was determined using the Scottish Index of Multiple Deprivation (SIMD) 2006 score (www.scotland.gov.uk/Topics/Statistics/SIMD) and categorised in quintiles, with quintile 1 representing the most affluent and quintile 5 representing the most deprived group. Habitual diet was assessed using a 120 item food-frequency questionnaire [25].

Anthropometry Height, body mass, circumferences at five sites (waist, hip, mid-upper arm, mid-thigh and mid-calf) and skinfolds at seven sites (biceps, triceps, subscapular, suprailiac, supraspinale, thigh and calf) were measured by the same trained investigator (J. Wilson) using international standard protocols [26] in all participants. The between-day coefficient of variation for all skinfold measurements was

<5%. Total body lean and fat masses were measured using air displacement plethysmography, with participants wearing only shorts or underwear (BOD POD body composition system, Life Measurement Instruments, CA, USA), as described previously [27].

Blood biochemistry and BP measurements Venous blood samples were obtained after an overnight fast of 10–12 h. Glucose, HbA_{1c}, total cholesterol, HDL-cholesterol, LDL-cholesterol, triacylglycerol, γ -glutamyltransferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and C-reactive protein (CRP) were analysed on the day of collection in the National Health Service Biochemistry Laboratory in Glasgow, using standard automated enzymatic (for glucose, lipids and liver function tests), immunoturbidimetric (CRP) and HPLC (HbA_{1c}) methods. This laboratory participates in the UK National External Quality Assessment Service (UKNEQAS) scheme and all tests had interassay CVs <5%. Plasma was stored at -80°C for subsequent measurement of insulin, using a commercially available ELISA (Mercodia, Uppsala, Sweden), in a single batch at the end of the study. HOMA-estimated insulin resistance (HOMA_{IR}) was calculated as previously described [28].

BP was measured after ≥ 15 min of seated rest using an automated BP monitor (Omron HEM705CP, Omron Healthcare UK Limited, Milton Keynes, UK), which had been validated according to the European Society of Hypertension International Protocol [29]. The mean of four BP readings was used in analysis.

Determination of cardiorespiratory fitness All participants had a clinical assessment and resting ECG prior to undertaking the exercise test to ensure no contraindications to maximal exercise. $\dot{V}\text{O}_{2\text{max}}$ was determined by a continuous incremental uphill walking protocol [30], with 1 min expired air samples taken continuously using Douglas bags and heart rate monitored by short-range telemetry. Achievement of $\dot{V}\text{O}_{2\text{max}}$ was verified by volitional exhaustion and confirmed by the achievement of a minimum of two of the three following criteria: (1) respiratory exchange ratio (RER) ≥ 1.15 ; (2) heart rate $\geq 90\%$ of age-predicted maximum; and (3) an increase in $\dot{V}\text{O}_2$ of $<2.1 \text{ ml kg}^{-1} \text{ min}^{-1}$ between the last two bags of collected expired air [30, 31].

Measurement of physical activity Participants wore accelerometers (GT3X+ or ActiTrainer; ActiGraph LLC, Pensacola, FL, USA) on the left or right hip at all times, except when showering, swimming and sleeping, for 7 consecutive days to objectively assess physical activity levels. Vertical axis accelerometer readings were summarised in 60 s epochs and Freedson cut-points were used to define intensity domains [32]. Data from participants with at least 10 h of daily

accelerometer wear time for 4 days were included in the analysis. Non-wear was defined by intervals of ≥ 60 min of zero activity counts [33]. Wear time was calculated by subtracting non-wear time from 24 h. Activity count values of $<100 \text{ count min}^{-1}$ were defined as sedentary behaviour [34].

Data analysis The sample size for the CURVES study was based on the assumption that prevalence of carotid plaques (to be reported elsewhere) would be 50% higher in South Asians than Europeans. Having 100 participants in each group would enable this difference to be detected with 80% power at $p < 0.05$. Based on our previously published data [6], this number of participants would enable detection of differences of ~ 0.4 units, $\sim 3 \text{ ml kg}^{-1} \text{ min}^{-1}$ and $\sim 2 \text{ kg}$ in HOMA_{IR}, $\dot{V}\text{O}_{2\text{max}}$ and fat mass, respectively, with the same power, between the South Asian and European groups.

Summary statistics are presented for all variables for both South Asian and European men. Continuous variables were compared between the ethnic groups by *t* tests (or Wilcoxon rank sum test for non-normally distributed variables) and Fisher's exact test for categorical variables.

Factor analysis was used to reduce the number of anthropometric variables into underlying latent factors [35]. Three factors emerged relating to 'total adiposity' (identified by biceps, triceps, subscapular, supraspinale, suprailiac, thigh and calf skinfolds, and fat mass), 'body size' (height, lean mass and hip, mid-thigh and mid-calf circumferences) and 'central adiposity' (waist circumference and waist-to-hip ratio). Factor loadings are shown in electronic supplementary material (ESM) Table 1. A summary measure was calculated to describe each factor. Each variable was standardised (by subtracting the mean and dividing by the SD), averaged according to the factor analysis groups and then standardised again. Initially, linear regression models, adjusted for ethnicity, were used to assess associations between total adiposity, body size, central adiposity, physical activity, sedentary behaviour and fitness (expressed as standardised measures) on HOMA_{IR} and fasting glucose concentration. The effects of potential confounding covariates (age, education, SES, smoking, alcohol, diabetes family history) on HOMA_{IR} and fasting glucose concentration were also assessed. Both outcome variables were log transformed (to base *e*) for analysis. The relative effects of ethnicity on HOMA_{IR} and glucose were then calculated: when it was the only predictor in the model; after separate adjustment for total adiposity, body size, central adiposity, physical activity, sedentary behaviour and fitness; and in the final model, including adjustment for all of the above variables that significantly influenced the ethnicity effect. Thus, this analysis enabled determination of the extent to which differences in HOMA_{IR} and fasting glucose concentration between South Asians and Europeans could be explained by body composition, fitness and

Table 1 Demographic and metabolic variables for South Asian and European men

Variable	South Asian (n=87)	European (n=99)	p value
Demographic and lifestyle variables			
Age (years)	48.3 (6.8)	49.7 (6.8)	0.162
Body mass (kg)	82.0 (12.1)	85.7 (13.9)	0.056
Height (m)	1.74 (0.07)	1.79 (0.06)	<0.001
BMI (kg/m ²)	27.1 (3.8)	26.9 (4.3)	0.700
Years in education	15.4 (3.4)	14.4 (3.2)	0.042
SIMD quintile, n (%)			0.751
1	6 (6.9)	7 (7.1)	
2	10 (11.5)	13 (13.1)	
3	16 (18.4)	19 (19.2)	
4	23 (26.4)	18 (18.2)	
5	32 (36.8)	42 (42.4)	
Smoking status, n (%)			<0.001
Never smoker	71 (81.6)	54 (54.5)	
Ex-smoker	5 (5.7)	35 (35.4)	
Current	11 (12.6)	10 (10.1)	
Alcohol consumption ^a , n (%)			<0.001
None	81 (93.1)	10 (10.2)	
≤20 units per week	4 (4.6)	69 (70.4)	
≥21 units per week	2 (2.3)	19 (19.4)	
Parental diabetes status ^a , n (%)			<0.001
Yes	50 (57.5%)	12 (12.2%)	
Sibling diabetes status ^a , n (%)			0.002
Yes	13 (14.9%)	2 (2.0%)	
Metabolic variables			
Glucose (mmol/l)	5.3 (4.9, 5.7)	5.1 (4.8, 5.4)	0.018 ^c
HbA _{1c} (mmol/mol) ^b	39.0 (37.0, 41.0)	36.0 (33.0, 38.0)	<0.001 ^c
HbA _{1c} (%) ^b	5.7 (5.5, 5.9)	5.4 (5.2, 5.6)	<0.001 ^c
Insulin (pmol/l) ^b	88.9 (69.5, 119.5)	54.2 (36.8, 79.9)	<0.001 ^c
HOMA _{IR} ^b	3.0 (2.4, 4.2)	1.8 (1.1, 2.6)	<0.001 ^c
Total cholesterol (mmol/l)	5.4 (1.0)	5.6 (1.0)	0.107
HDL-cholesterol (mmol/l)	1.1 (1.0, 1.3)	1.3 (1.1, 1.6)	<0.001 ^c
LDL-cholesterol (mmol/l)	3.5 (0.9)	3.6 (0.8)	0.458
Triacylglycerol (mmol/l)	1.4 (1.0, 2.2)	1.3 (0.9, 1.8)	0.135 ^c
AST (μkat/l)	0.39 (0.11)	0.42 (0.14)	0.100
ALT (μkat/l)	0.43 (0.35, 0.59)	0.43 (0.33, 0.59)	0.857 ^c
GGT (μkat/l)	0.50 (0.37, 0.71)	0.47 (0.34, 0.73)	0.572 ^c
CRP (nmol/l) ^a	17.1 (10.5, 38.1)	10.5 (5.7, 23.8)	0.003 ^c
Systolic BP (mmHg)	126.3 (15.4)	127.5 (12.9)	0.568
Diastolic BP (mmHg)	77.8 (9.1)	74.9 (7.2)	0.018

Values are mean (SD) for normally distributed variables with *p* values calculated by *t* tests, and median (interquartile range) for non-normally distributed variables with *p* values calculated by Wilcoxon test; *p* values for categorical variables were calculated by Fisher's exact test

^a *n*=98 for Europeans

^b *n*=86 for South Asians

^c Wilcoxon test

physical activity variables. The absolute differences in geometric means for HOMA_{IR} and fasting glucose concentration between the groups were calculated for each model, using the mean value for continuous predictors and the reference level for any categorical variables; 95% CIs for the differences were derived by bootstrapping. The percentage change in the relative percentile difference between South Asians

and Europeans in HOMA_{IR} and fasting glucose concentration were calculated with 95% CIs and *p* values derived by bootstrapping (reductions greater than 100% describe a change in direction of the effect).

The statistical software package R for Windows v2.14 (<http://cran.r-project.org/>) was used for all analysis. Statistical significance was accepted at *p*<0.05.

Results

Demographic and metabolic variables Thirteen South Asian men and one European man who completed the study were subsequently noted to have HbA_{1c} concentrations >6.5% (>48 mmol/mol) and/or fasting glucose concentrations >7 mmol/l, indicating possible undiagnosed diabetes. Their data were excluded from the analyses. Our final data set therefore included 87 South Asian and 99 European men. Demographic and metabolic variables for the final South Asian and European cohorts are presented in Table 1. There were no differences between groups in age or BMI, but the South Asians were shorter than the Europeans. South Asians also had completed more years in education, were less likely to smoke or consume alcohol and were more likely to have a

parent or sibling with type 2 diabetes. There were no differences in SES. South Asians had significantly higher glucose, HbA_{1c}, insulin, HOMA_{IR}, CRP and diastolic blood pressure, and lower HDL-cholesterol than the Europeans.

Body composition, fitness and physical activity variables Body composition, fitness and physical activity variables are presented in Table 2. There were no differences in waist or hip circumferences between the South Asian and European groups, but waist-to-hip ratio was higher in the South Asians. South Asians also had a smaller mid-thigh circumference, and higher values for all skinfold thicknesses than the Europeans. Lean mass was lower and fat mass and percentage body fat were higher in the South Asians. Total adiposity and central adiposity factors were higher and the body size factor

Table 2 Body composition, fitness, and physical activity variables for South Asian and European men

Variable	South Asian (n=87)	European (n=99)	p value
Anthropometric			
Body circumference			
Waist (cm)	97.3 (10.9)	95.6 (11.2)	0.315
Hips (cm)	99.5 (6.6)	100.5 (7.1)	0.336
Waist-to-hip ratio	0.98 (0.07)	0.95 (0.06)	0.009
Mid-upper arm (cm)	34.5 (8.2)	33.4 (3.3)	0.238
Mid-thigh (cm)	52.6 (4.3)	54.0 (4.0)	0.030
Mid-calf (cm)	37.7 (3.4)	38.6 (4.1)	0.101
Skinfold thickness			
Biceps (mm) ^a	8.0 (3.6)	6.8 (2.9)	0.015
Triceps (mm)	16.4 (5.8)	12.6 (4.3)	<0.001
Subscapular (mm) ^{a,b}	25.7 (7.3)	18.3 (7.1)	<0.001
Suprailiac (mm) ^{c,d}	23.4 (6.2)	18.2 (6.2)	<0.001
Supraspinale (mm)	18.0 (6.6)	12.6 (5.4)	<0.001
Thigh (mm) ^a	19.1 (7.9)	14.6 (5.7)	<0.001
Calf (mm) ^c	13.0 (5.4)	10.4 (4.2)	<0.001
Fat and lean mass			
Lean mass (kg) ^a	57.2 (6.4)	63.3 (7.1)	<0.001
Fat mass (kg) ^a	24.4 (9.0)	21.8 (9.7)	0.058
Percentage body fat ^a	29.2 (7.4)	24.8 (7.4)	<0.001
Summary anthropometric factors			
Total adiposity ^f (standardised units)	0.4 (1.0)	-0.3 (0.9)	<0.001
Body size ^g (standardised units)	-0.3 (0.9)	0.3 (1.0)	<0.001
Central adiposity ^h (standardised units)	0.1 (1.0)	-0.1 (1.0)	0.058
Fitness variables			
$\dot{V}O_{2max}$ (l/min) ^a	2.6 (0.4)	3.4 (0.6)	<0.001
$\dot{V}O_{2max}$ (ml kg ⁻¹ min ⁻¹) ^a	31.5 (5.8)	39.6 (7.5)	<0.001
$\dot{V}O_{2max}$ (ml/[kg lean mass] ⁻¹ min ⁻¹) ⁱ	44.7 (6.4)	53.0 (7.8)	<0.001
Physical activity variables			
Sedentary (% of wear time) ^j	66.5 (9.5)	64.2 (9.1)	0.136
Light physical activity (% of wear time) ^j	30.4 (9.2)	30.8 (8.1)	0.789
MVPA (% of wear time) ^j	2.8 (1.7, 4.1)	4.1 (3.0, 6.8)	<0.001 ^k
Total accelerometer wear time (min/day) ^j	824.5 (85.1)	863.0 (74.2)	0.003

Values are mean (SD) for normally distributed variables with p values calculated by t tests, and median (interquartile range) for non-normally distributed variables with p values calculated by Wilcoxon test

^a n=98 for Europeans; ^b n=82 for South Asians; ^c n=95 for Europeans; ^d n=84 for South Asians; ^e n=86 for South Asians

^f Derived from biceps, triceps, subscapular, supraspinale, suprailiac, thigh, and calf skinfolds and fat mass

^g Derived from height, lean mass and hip, mid-thigh and mid-calf circumferences

^h Derived from waist circumference and waist-to-hip ratio

ⁱ n=97 for Europeans; ^j n=83 for Europeans and n=75 for South Asians

^k Wilcoxon test

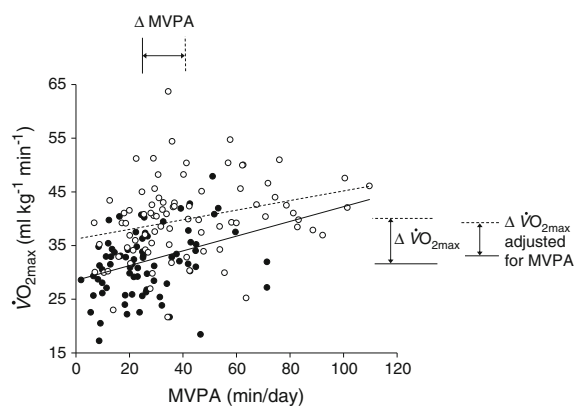


Fig. 1 Relationship between maximal oxygen uptake ($\dot{V}O_{2\max}$) and MVPA in South Asian (black circles, solid line) and European (white circles, dotted line) men. Solid and dotted vertical bars indicate mean MVPA levels in South Asian and European men, respectively; the horizontal arrow shows the mean difference in MVPA between ethnic groups. Solid and dotted horizontal bars, with corresponding vertical arrows, indicate mean $\dot{V}O_{2\max}$ values in South Asian and European men, respectively, and the mean ethnic difference, both unadjusted and adjusted for MVPA

was lower in South Asians than Europeans. Cardiorespiratory fitness (as assessed by $\dot{V}O_{2\max}$) was lower in South Asians than Europeans, irrespective of whether this was expressed in absolute terms (i.e. l/min) (lower on average by 24%), per kg body mass (by 21%) or per kg lean mass (by 16%).

South Asians also engaged in less moderate-to-vigorous physical activity (MVPA) than Europeans: the proportion of time spent in MVPA was, on average, ~32% lower in South Asians than Europeans. This equated to South Asians engaging

in ~23 min MVPA/day compared with ~34 min/day for the Europeans. There were significant correlations between $\dot{V}O_{2\max}$ (in $\text{ml kg}^{-1} \text{min}^{-1}$) and log MVPA in both South Asians ($r=0.326$, $p=0.004$) and Europeans ($r=0.326$, $p=0.003$). However, the lower $\dot{V}O_{2\max}$ values in South Asians could not be explained by their lower levels of physical activity: South Asians' $\dot{V}O_{2\max}$ values were lower than those of Europeans across the range of MVPA levels, and their $\dot{V}O_{2\max}$ values remained significantly lower than Europeans after adjustment for MVPA (Fig. 1). Reported energy intake (expressed per kg body mass) did not differ between the Europeans and South Asians (83.2 ± 25.1 vs 78.2 ± 27.2 $\text{kJ kg}^{-1} \text{day}^{-1}$, $p=0.21$). There were also no differences in reported protein, carbohydrate or fat intakes between the two groups (data not shown), but reported alcohol intake was higher in the Europeans than the South Asians (22.1 ± 18.3 vs 1.2 ± 6.0 g/day, $p<0.001$).

Associations between anthropometric, physical activity and fitness variables with HOMA_{IR} and fasting glucose concentration Table 3 shows ethnicity-adjusted relative effects of anthropometric, physical activity and fitness variables on HOMA_{IR} and fasting glucose concentration. HOMA_{IR} increased with increasing total adiposity, body size, central adiposity and sedentary time and decreased with increasing MVPA and $\dot{V}O_{2\max}$. Fasting glucose concentration increased with increasing total adiposity and decreased with increasing $\dot{V}O_{2\max}$. For these analyses, $\dot{V}O_{2\max}$ was expressed in $\text{ml kg}^{-1} \text{min}^{-1}$, but results were similar when $\dot{V}O_{2\max}$ was expressed in l/min or in $\text{ml kg lean mass}^{-1} \text{min}^{-1}$. The effects of potential confounding covariates on HOMA_{IR} and fasting

Table 3 Associations (as relative effects) between HOMA_{IR} and fasting glucose concentration with standardised anthropometric, physical activity and fitness variables

Predictor	HOMA _{IR}		Fasting glucose concentration	
	Relative effect estimate (95% CI)	<i>p</i> value	Relative effect estimate (95% CI)	<i>p</i> value
Anthropometric variables				
Total adiposity ^a	1.40 (1.30, 1.50)	<0.001	1.02 (1.00, 1.03)	0.013
Body size ^b	1.21 (1.12, 1.31)	<0.001	1.00 (0.99, 1.02)	0.666
Central adiposity ^c	1.40 (1.31, 1.49)	<0.001	1.01 (1.00, 1.03)	0.075
Physical activity variables				
MVPA	0.86 (0.79, 0.94)	0.001	0.99 (0.97, 1.01)	0.263
Sedentary	1.10 (1.01, 1.20)	0.024	1.01 (0.99, 1.02)	0.299
Fitness variables				
$\dot{V}O_{2\max}$ ($\text{ml kg}^{-1} \text{min}^{-1}$)	0.74 (0.68, 0.80)	<0.001	0.98 (0.97, 1.00)	0.020

Relative effects (ratios of geometric means) are for a 1 SD change in the predictor variable, adjusted for ethnicity

Values are presented with 95% CI and *p* values

^a Derived from biceps, triceps, subscapular, supraspinale, suprailiac, thigh and calf skinfolds, and fat mass

^b Derived from height, lean mass and hip, mid-thigh and mid-calf circumferences

^c Derived from waist circumference and waist-to-hip ratio

Table 4 Relative and absolute effects of ethnicity on HOMA_{IR}, unadjusted and adjusted by anthropometric, physical activity and fitness variables

Variable	n	Relative ethnicity effect estimate for HOMA _{IR}		Absolute difference in HOMA _{IR} between Europeans and South Asians (HOMA _{IR} units)		Percentage change in ethnicity difference with adjustment ^c			
		Unadjusted ^a	Adjusted for predictor variable	Unadjusted ^b	Adjusted for predictor variable	Percentage change estimate	p value		
Anthropometric variables									
Total adiposity ^d	185	1.67 (1.42, 1.96)	<0.001	1.32 (1.15, 1.53)	<0.001	1.19 (0.81, 1.60)	0.64 (0.33, 0.98)	-51.7 (-80.3, -29.5)	<0.001
Body size ^e	185	1.67 (1.42, 1.96)	<0.001	1.86 (1.59, 2.18)	<0.001	1.19 (0.81, 1.60)	1.45 (1.05, 1.90)	28.5 (11.5, 48.3)	<0.001
Central adiposity ^f	185	1.67 (1.42, 1.96)	<0.001	1.53 (1.34, 1.74)	<0.001	1.19 (0.81, 1.60)	0.98 (0.68, 1.29)	-21.2 (-46.6, 2.3)	0.080
Physical activity variables									
MVPA	157	1.57 (1.32, 1.86)	<0.001	1.41 (1.18, 1.68)	<0.001	1.05 (0.65, 1.50)	0.80 (0.39, 1.23)	-27.5 (-45.9, -10.7)	<0.001
Sedentary	157	1.57 (1.32, 1.86)	<0.001	1.53 (1.29, 1.82)	<0.001	1.05 (0.65, 1.50)	1.00 (0.59, 1.40)	-6.0 (-19.1, 2.0)	0.162
Fitness variables									
$\dot{V}O_{2\max}$ (ml kg ⁻¹ min ⁻¹)	184	1.66 (1.41, 1.95)	<0.001	1.22 (1.03, 1.44)	0.022	1.18 (0.80, 1.58)	0.44 (0.08, 0.84)	-67.5 (-90.9, -45.1)	<0.001
All statistically significant factors									
Total adiposity+body size+MVPA + $\dot{V}O_{2\max}$	156	1.56 (1.31, 1.85)	<0.001	1.09 (0.91, 1.31)	0.332	1.04 (0.61, 1.48)	0.20 (-0.21, 0.63)	-83.4 (-118.9, -50.1)	<0.001

Estimates for the effect of ethnicity on HOMA_{IR}, expressed as a relative effect (ratios of geometric means); in terms of absolute difference in the geometric mean (in HOMA_{IR} units); and the percentage change between these effects after adjustment are presented with 95% CIs and p values

^a Unadjusted relative ethnicity effect (for South Asians compared with Europeans)

^b Unadjusted ethnicity effect in absolute HOMA_{IR} units

^c Percentage change in unadjusted ethnicity effect estimate to adjusted model effect

^d Derived from biceps, triceps, subscapular, supraspinale, suprailiac, thigh and calf skinfolds, and fat mass

^e Derived from height, lean mass and hip, mid-thigh and mid-calf circumferences

^f Derived from waist circumference and waist-to-hip ratio

glucose concentration are shown in ESM Table 2. HOMA_{IR} was higher in ex-smokers (but not current smokers) than non-smokers (by 26% [95% CI 2%, 56%; $p=0.03$]). Other than this, none of the measured covariates was significantly associated with HOMA_{IR} or fasting glucose concentration.

Contribution of anthropometric, physical activity and fitness variables to the difference in HOMA_{IR} between Europeans and South Asians Table 4 shows the effect of ethnicity, in relative and absolute terms, on HOMA_{IR} , unadjusted and in models adjusted for anthropometric, physical activity and fitness variables. In the unadjusted analysis, HOMA_{IR} values in South Asians were 67% (95% CI 42%, 96%, $p<0.001$) higher than the values observed in Europeans. Ethnicity contributed 18% of the total variance in HOMA_{IR} . Adjusting for total adiposity attenuated the difference in HOMA_{IR} between ethnic groups by 51.7% (29.5%, 80.3%), whereas adjusting for body size increased the difference by 28.5% (11.5%, 48.3%). Adjusting for MVPA reduced the difference in HOMA_{IR} between South Asians and Europeans by 27.5% (10.7%, 45.9%). However, the difference in $\dot{V}\text{O}_{2\text{max}}$ between South Asians and Europeans explained more of the difference in HOMA_{IR} than any other variable: adjustment for $\dot{V}\text{O}_{2\text{max}}$ attenuated the difference in HOMA_{IR} between ethnic groups by 67.5% (45.1%, 90.9%). This is further illustrated in Fig. 2. Adjustment for central adiposity or sedentary time did not significantly alter the ethnicity effect on HOMA_{IR} . Simultaneously adjusting for the four variables that significantly changed the ethnicity effect (total adiposity, body size, MVPA and $\dot{V}\text{O}_{2\text{max}}$) attenuated the difference in HOMA_{IR} between South Asians and Europeans by 83.4% (50.1%, 118.9%). Repeating the analyses after adjustment for

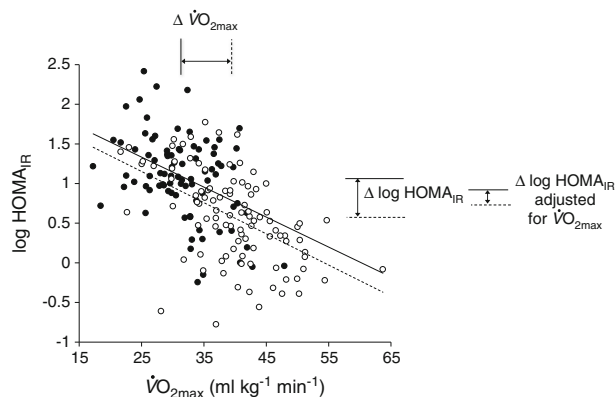


Fig. 2 Relationship between HOMA_{IR} and $\dot{V}\text{O}_{2\text{max}}$ in South Asian (black circles, solid line) and European (white circles, dotted line) men. HOMA_{IR} values are displayed as natural logarithms. Solid and dotted vertical bars indicate mean $\dot{V}\text{O}_{2\text{max}}$ values in South Asian and European men, respectively; the horizontal arrow shows the mean difference in $\dot{V}\text{O}_{2\text{max}}$ between ethnic groups. Solid and dotted horizontal bars, with corresponding vertical arrows, indicate mean HOMA_{IR} values in South Asian and European men and the mean ethnic difference, both unadjusted and adjusted for $\dot{V}\text{O}_{2\text{max}}$

smoking, alcohol consumption, education and SES produced similar findings (ESM Table 3). In these confounder-adjusted analyses, the difference in $\dot{V}\text{O}_{2\text{max}}$ between South Asians and Europeans explained 77.8% (38.4%, 132.2%) of the ethnic difference in HOMA_{IR} , and the contribution of total adiposity to the difference in HOMA_{IR} between the ethnic groups was attenuated slightly to 41.3% (0.5%, 95.7%).

Contribution of anthropometric, physical activity and fitness variables to the difference in fasting glucose concentration between Europeans and South Asians Table 5 presents similar data for the fasting glucose concentration. In the unadjusted analysis, fasting glucose concentrations in South Asians were 3% (95% CI 1%, 6%; $p=0.017$) higher than in Europeans. Ethnicity contributed 3% of the variance in fasting glucose. Adjusting for total adiposity attenuated the ethnic difference in fasting glucose by 39.1% (9.4%, 76.1%). Similar to effects on HOMA_{IR} , $\dot{V}\text{O}_{2\text{max}}$ explained more of the difference in fasting glucose concentration between South Asians and Europeans than any other variable, with adjustment for $\dot{V}\text{O}_{2\text{max}}$ attenuating the ethnic difference by 60.7% (9.2%, 111.0%). The ethnicity effect for fasting glucose concentration was not significantly influenced by body size, central adiposity, MVPA or sedentary time. Simultaneously adjusting for total adiposity and $\dot{V}\text{O}_{2\text{max}}$ attenuated the ethnic difference in fasting glucose by 63.4% (8.2%, 114.6%). Repeating the analyses after adjustment for smoking, alcohol consumption, education and SES produced essentially similar findings (ESM Table 4), with $\dot{V}\text{O}_{2\text{max}}$ still explaining more of the difference in fasting glucose concentration between the ethnic groups than other any variable (−41.6% [−232.0%, −1.7%]). In these confounder-adjusted analyses no other variables significantly contributed to the ethnicity difference.

Discussion

The main novel finding of this study was that low cardiovascular fitness, as measured by the gold-standard maximal incremental treadmill test, was the single most important factor associated with the increased insulin resistance and fasting glycaemia observed in middle-aged South Asian compared with European men living in the UK. Ethnicity explained 18% of the variance in HOMA_{IR} , with HOMA_{IR} values being 67% higher in South Asians than Europeans. South Asians' lower $\dot{V}\text{O}_{2\text{max}}$ levels (statistically) explained more than two-thirds of this ethnic difference. The ethnic difference in fasting glucose concentration was less pronounced. Ethnicity explained 3% of the variance in fasting glucose, and values were 3% higher in South Asians than Europeans: nevertheless over 60% of the ethnic difference in

Table 5 Relative and absolute effects of ethnicity on fasting glucose concentration, unadjusted and adjusted by anthropometric, physical activity and fitness variables

Variable	n	Relative ethnicity effect estimate for fasting glucose concentration		Absolute difference in fasting glucose concentration between Europeans and South Asians (mmol/l)		Percentage change in ethnicity difference with adjustment ^c			
		Unadjusted ^a	p value	Adjusted for predictor variable	p value	Unadjusted ^b	Adjusted for predictor variable	Unadjusted ^b	p value
Anthropometric variables									
Total adiposity ^d	186	1.03 (1.01, 1.06)	0.017	1.02 (0.99, 1.05)	0.163	0.18 (0.03, 0.33)	0.11 (-0.05, 0.27)	-39.1 (-76.1, -9.4)	0.008
Body size ^e	186	1.03 (1.01, 1.06)	0.017	1.04 (1.01, 1.07)	0.016	0.18 (0.03, 0.33)	0.19 (0.03, 0.33)	5.4 (-15.9, 26.4)	0.600
Central adiposity ^f	186	1.03 (1.01, 1.06)	0.017	1.03 (1.00, 1.06)	0.033	0.18 (0.03, 0.33)	0.16 (0.01, 0.30)	-10.6 (-31.7, 1.8)	0.128
Physical activity variables									
MVPA	158	1.04 (1.01, 1.07)	0.016	1.03 (1.00, 1.07)	0.063	0.20 (0.04, 0.36)	0.16 (0.00, 0.33)	-18.0 (-48.6, 10.6)	0.220
Sedentary	158	1.04 (1.01, 1.07)	0.016	1.04 (1.01, 1.07)	0.023	0.20 (0.04, 0.36)	0.19 (0.03, 0.34)	-5.2 (-19.2, 5.5)	0.406
Fitness variables									
$\dot{V}O_{2\max}$ (ml kg ⁻¹ min ⁻¹)	185	1.03 (1.00, 1.06)	0.023	1.01 (0.98, 1.05)	0.430	0.17 (0.02, 0.30)	0.07 (-0.09, 0.22)	-60.7 (-111.0, -9.2)	0.028
All statistically significant factors									
Total adiposity + $\dot{V}O_{2\max}$	185	1.03 (1.00, 1.06)	0.023	1.01 (0.98, 1.04)	0.460	0.17 (0.02, 0.30)	0.06 (-0.09, 0.22)	-63.4 (-114.6, -8.2)	0.030

Estimates for the effect of ethnicity on fasting glucose concentration, expressed as a relative effect (ratios of geometric means); in terms of absolute difference in the geometric mean (in mmol/l); and the percentage change between these effects after adjustment are presented with 95% CIs and *p* values

^aUnadjusted relative ethnicity effect (for South Asians compared with Europeans)

^bUnadjusted ethnicity effect in mmol/l

^cPercentage change in unadjusted ethnicity effect estimate to adjusted model effect

^dDerived from biceps, triceps, subscapular, supraspinale, suprailiac, thigh and calf skinfolds, and fat mass

^eDerived from height, lean mass and hip, mid-thigh and mid-calf circumferences

^fDerived from waist circumference and waist-to-hip ratio

fasting glucose (~ 0.1 mmol/l) could be explained by $\dot{V}O_{2\max}$. Higher total adiposity and lower MVPA in South Asians were also associated with their greater HOMA_{IR}; their increased total adiposity was also associated with their higher fasting glucose values. Fitness, anthropometric and physical activity variables together explained over four-fifths of the increased insulin resistance and three-fifths of the increased glycaemia observed in South Asians.

The finding that greater total adiposity explained about half South Asians' increased insulin resistance and two-fifths of their increased fasting glycaemia compared with Europeans is consistent with other reports [5, 13, 14], although interestingly South Asians' smaller body size acted in the opposite direction, appearing to attenuate the difference in HOMA_{IR} between the groups. Furthermore, our findings demonstrate, using robust objective measures, that levels of physical activity were significantly lower in South Asians than Europeans in our sample, which is consistent with the suggestions from previous self-reported data [17–20], and reveals for the first time that this contributes to their greater insulin resistance. However, the most striking finding from this study is the extent to which lower cardiorespiratory fitness was associated with South Asians' insulin-resistant phenotype. This is consistent with data from animal models that have demonstrated a causal link between low fitness and insulin resistance [36] and with epidemiological data reporting a 2.6-fold increased risk of incident type 2 diabetes, independent of BMI, in men with low cardiorespiratory fitness levels compared with high levels [10]. Importantly, the present data demonstrate that although fitness increases with increasing physical activity, South Asians' lower $\dot{V}O_{2\max}$ values could not be explained simply by their lower physical activity levels. South Asians had lower fitness levels than Europeans at all levels of physical activity, and adjusting for MVPA only modestly attenuated the ethnic difference in $\dot{V}O_{2\max}$ (see Fig. 1). Interestingly, recent data from the National Health and Nutrition Examination Survey (NHANES) support the suggestion of innate differences in fitness between ethnic groups, with Ceaser and colleagues reporting systematic differences in $\dot{V}O_{2\max}$ between Mexican Americans (highest), non-Hispanic whites and non-Hispanic blacks (lowest) that were independent of time spent in (self-reported) physical activity and demographic factors [37]. There is a strong heritable component to $\dot{V}O_{2\max}$, with heritability estimates in this trait of up to 50% [38, 39]; thus, it seems likely that there will be a genetic (and/or early origins) contribution to the lower $\dot{V}O_{2\max}$ values in South Asians. We have recently reported that South Asians have a reduced ability to oxidise fat during exercise compared with Europeans [6], suggesting that there may be innate differences in the physiology of South Asians compared with Europeans that may contribute to this effect. The fact that South Asians' increased insulin resistance and glycaemia is strongly associated with their lower fitness

levels, and that increasing physical activity is the only way to increase cardiorespiratory fitness, suggests that South Asians may need to engage in greater levels of physical activity than Europeans to achieve the same levels of cardiorespiratory fitness and minimise their metabolic risk. This has potential implications for physical activity guidance, which, at present, does not take ethnicity into account. Recent consensus statements have recommended that the BMI threshold for obesity in South Asian populations should be lowered from 30 kg/m² to BMI 25 kg/m² [40, 41], in recognition of the substantially lower BMIs that are needed in South Asians to confer equivalent cardiometabolic-risk-factor profiles to those observed in populations of white European origin [4, 42]. The present data suggest that differential physical activity guidance for South Asians may also be needed. Larger epidemiological studies, and intervention trials, comparing the dose-response relationship between (objectively measured) physical activity and risk of cardiometabolic disease in South Asians and Europeans are urgently needed to enable appropriate levels of physical activity to minimise risk in South Asian populations to be robustly quantified.

This study has a number of strengths. We were initially rigorous to exclude those with known diabetes and those with potential undiagnosed diabetes (remarkably, 13% of South Asian men [vs 1% of European men]) from further analysis, to prevent potential confounding. This is the largest study to compare objectively measured physical activity and cardiorespiratory fitness between South Asian and European men. Thus, differences in fitness and activity between these groups and the contribution of these factors to insulin resistance and glycaemia can be robustly assessed from the present data. Furthermore, we measured a wide range of adiposity variables and used factor analysis to derive robust summary measures of body size and composition to enable us to determine which specific features of South Asians' greater adiposity contributed to their increased insulin resistance and glycaemia. The groups were well-matched for age, BMI and SES. While South Asians spent more years in education, smoked less and drank less alcohol than the Europeans, adjusting for these factors did not change the key study outcomes: difference in $\dot{V}O_{2\max}$ remained the most important factor associated with South Asians' greater insulin resistance after adjustment for these potential confounders. However, the study does have limitations. By the nature of the recruitment methods, the study cohort represents a self-selected group, and thus a degree of caution is warranted in extrapolating the findings to the general UK South Asian population. However, as the findings with respect to fitness, physical activity, adiposity and metabolic variables in South Asians are fully consistent with the body of previously published data on this topic, this seems unlikely to have introduced substantial bias into the findings. We assessed insulin resistance using HOMA_{IR}, as the size of this single-

centre study made use of the gold-standard euglycaemic–hyperinsulinaemic clamp unfeasible. Similarly, we assessed glycaemia from fasting glucose concentrations; we chose not to use HbA_{1c} as a marker of long-term glycaemia in our analyses because of potential confounding from known ethnic differences in glycation rates independent of glycaemia [43]. Finally, the cross-sectional nature of the study, with simultaneous assessment of exposure and outcome variables, means that it is not possible to definitively exclude reverse causality as a potential influence on the findings.

In conclusion, the present findings show that low cardiorespiratory fitness is a key factor associated with the increased insulin resistance and fasting glycaemia in middle-aged South Asian, compared with European, men living in the UK. Although they were less physically active than their European counterparts, South Asians' lower fitness levels could not be explained by their lower physical activity levels, suggesting that low fitness is an innate feature of the South Asian phenotype. Though the observational nature of this study means that conclusions cannot be drawn about causality, the present data suggest that South Asians may need to engage in higher levels of physical activity than Europeans to overcome their lower innate fitness and the associated metabolic consequences. This raises the possibility that ethnicity-specific recommendations for physical activity, and thus prevention of diabetes, may be needed.

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Author contributions NG, NS and JMRG conceived and designed the study. NG and JW collected experimental data. NG, DP, AM, NS and JMRG analysed and interpreted data. NG, DP and JMRG drafted the manuscript. All authors critically revised the manuscript and approved the final version.

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